

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|--|---|--|
| Applicant's or agent's file reference AM100039/PCT | <div style="display: flex; justify-content: space-between;"> <div style="text-align: center;">FOR FURTHER ACTION</div> <div style="font-size: small;">see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</div> </div> | |
| International application No. PCT/US 00/ 17019 | International filing date (day/month/year) 20/06/2000 | (Earliest) Priority Date (day/month/year) 25/06/1999 |
| Applicant AMERICAN CYANAMID COMPANY et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17019

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/285 C07K1/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | US 5 780 601 A (GREEN BRUCE A ET AL) 14 July 1998 (1998-07-14) abstract column 4 column 14; claim 1 --- | 1-16 |
| X | EP 0 389 925 A (THE RESEARCH FOUNDATION OF THE STATE UNIVERSITY OF NEW YORK) 3 October 1990 (1990-10-03) abstract column 2 column 16-17; claims --- | 1-16 |
| A | US 5 681 570 A (YANG YAN-PING ET AL) 28 October 1997 (1997-10-28) --- -/-- | |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

17 October 2000

Date of mailing of the international search report

03/11/2000

Name and mailing address of the ISA

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Authorized officer

Cervigni, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/17019

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | REIS R VAN: "INDUSTRIAL SCALE HARVEST OF PROTEINS FROM MAMMALIAN CELL CULTURE BY TANGENTIAL FLOW FILTRATION" BIOTECHNOLOGY AND BIOENGINEERING. INCLUDING: SYMPOSIUM BIOTECHNOLOGY IN ENERGY PRODUCTION AND CONSERVATION, US, JOHN WILEY & SONS. NEW YORK, vol. 38, no. 4, 5 August 1991 (1991-08-05), pages 413-422, XP000216469 ISSN: 0006-3592 --- | |
| A | WERNER R.G. ET AL.: "PURIFICATION OF PROTEINS PRODUCED BY BIOTECHNOLOGICAL PROCESS" ARZNEIMITTEL-FORSCHUNG/DRUG RESEARCH (1988) 38/3 (422-428) ISSN 0004-4172, XP002150296 ----- | |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/17019

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| US 5780601 | A | 14-07-1998 | US 5601831 A | 11-02-1997 |
| | | | US 5955580 A | 21-09-1999 |
| | | | AT 110965 T | 15-09-1994 |
| | | | AT 195076 T | 15-08-2000 |
| | | | AU 648251 B | 21-04-1994 |
| | | | AU 5332690 A | 09-10-1990 |
| | | | CA 2047681 A | 10-09-1990 |
| | | | DE 69012318 D | 13-10-1994 |
| | | | DE 69012318 T | 09-03-1995 |
| | | | DE 69033600 D | 07-09-2000 |
| | | | DK 462210 T | 10-10-1994 |
| | | | EP 0462210 A | 27-12-1991 |
| | | | EP 0606921 A | 20-07-1994 |
| | | | ES 2063965 T | 16-01-1995 |
| | | | JP 2955014 B | 04-10-1999 |
| | | | JP 7508972 T | 05-10-1995 |
| | | | KR 188323 B | 01-06-1999 |
| | | | NO 913518 A | 29-10-1991 |
| | | | WO 9010458 A | 20-09-1990 |
| <hr/> | | | | |
| EP 0389925 | A | 03-10-1990 | AT 132160 T | 15-01-1996 |
| | | | CA 2012676 A | 29-09-1990 |
| | | | DE 69024392 D | 08-02-1996 |
| | | | DE 69024392 T | 25-07-1996 |
| | | | DK 78990 A | 30-09-1990 |
| | | | ES 2081864 T | 16-03-1996 |
| | | | IE 71949 B | 12-03-1997 |
| | | | JP 3175991 A | 31-07-1991 |
| | | | US 5300632 A | 05-04-1994 |
| <hr/> | | | | |
| US 5681570 | A | 28-10-1997 | AU 4325496 A | 31-07-1996 |
| | | | CA 2210139 A | 18-07-1996 |
| | | | WO 9621465 A | 18-07-1996 |
| | | | EP 0805691 A | 12-11-1997 |
| <hr/> | | | | |

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | | |
|---|---|---|---|
| Applicant's or agent's file reference AM100039/PCT | FOR FURTHER ACTION | | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/US00/17019 | International filing date (day/month/year) 20/06/2000 | Priority date (day/month/year) 25/06/1999 | |
| International Patent Classification (IPC) or national classification and IPC C07K14/285 | | | |
| Applicant AMERICAN CYANAMID COMPANY et al. | | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 4 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 15/01/2001 | Date of completion of this report 26.04.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer A. M. Merlos Telephone No. +49 89 2399 8559 |



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/17019

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):
- Description, pages:**

1-30 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/17019

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | |
|-------------------------------|------------------|
| Novelty (N) | Yes: Claims 1-16 |
| | No: Claims |
| Inventive step (IS) | Yes: Claims 1-16 |
| | No: Claims |
| Industrial applicability (IA) | Yes: Claims 1-16 |
| | No: Claims |

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/17019

V

1. Novelty and Inventive Step

The present invention is concerned with a process for extracting native or recombinantly expressed gram-negative inner and outer membrane proteins from bacteria by differential detergent tangential flow diafiltration, in particular recombinant lipidated outer membrane protein P4 and recombinant lipidated outer membrane protein P6 of *H. influenzae*. Tangential flow diafiltration was used in the development of a process for large scale harvest of biologically active proteins from mammalian cell cultures (Biotechn. & Bioeng., 38, 1991, no. 4, van Reis, R. et al.).

- 1.1 Documents US 5,780,601 and EP 0 389 925, both describe methods for extraction of *H. influenzae* outer membrane protein which include multiple centrifugation steps. The latter are however avoided by the method disclosed in the present application. Therefore, claims 1-16 are considered to refer to a novel alternative (Art. 33(2)PCT).
- 1.2 Taking further into consideration that the present method was not derivable in an obvious manner from any of the available prior art documents, neither when taken alone nor when combined, an inventive step may also be acknowledged (Art. 33(3) PCT).

VIII

2. Clarity

- 2.1 It appears that claim 6 erroneously refers back to claim 3 (should probably refer to claim 5?).
- 2.2 It is further noted that according to the European Guidelines C III-4.5 (b), (EPC), the use of trademarks and similar expressions in claims should not be allowed unless their use is unavoidable.